DISCUSSION
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The present study was carried out in the department of Pediatrics, M.L.B. Medical College, Hospital, Jhansi, over a period of two years from August, 1991 to July, 1993.

The study was aimed to evaluate the clinical, pathological and immunological changes associated with nephrotic syndrome in children of this region. It was our endeavour to study response pattern to steroid therapy. Besides, clinico-pathological correlation it was also our aim to identify the factors by which one can predict the response pattern of steroids, or identify frequent relapsers.

A total of 65 cases of nephrotic syndrome were examined in the present study. The incidence of nephrotic syndrome among total pediatric admissions was observed to be 1.62%.

As also observed by earlier workers, it was found to be the commonest nephrotic entity in children presenting with renal disease (72.2%).

In our study we observed a preponderance of male children. Male : female ratio was observed to be 1.8 : 1. Similarly higher incidence of male children in nephrotic syndrome has been reported by Mc Enery et al (1982) and Saxena et al (1988), viz 2:1, 2.5:1 and 3:1 respectively. Prasad et al (1985) reported M : F ratio to be 1 : 1.
Mc Enery (1982) however reported this ratio to be 1:1 in adolescence. Heymann et al (1972) reported male : female ratio to be 1 : 1.

Concordance that had been described in monozygotic but not in non zygotic twin, suggested existence of undefined genetic factors. Male preponderance suggest some degree of X linked linkage (Norio et al, 1963).

The tendency towards small family size perhaps has caused non recognition of existence of X linked form of nephrosis. This entity may particularly account for male preponderance (Awadalla et al, 1989).

Many workers have reported increased incidence of nephrotic syndrome in sibs of affected child. Habib et al (1968) and (1973); Moncrieff et al (1973), Robin et al (1981) and Elzonski (1984) observed familial tendency to acquire nephrotic syndrome in 2-8%, 3-5%, 3.3%, 3.3% and 2.7% respectively. Michael et al (1974) reported incidence 1000 times greater, the incidence of nephrotic syndrome in sibs. But none of the sibs or members of the family of present study group were found to be suffering from nephrotic syndrome.

Further an attempt was made to categorise the various cases of nephrotic syndrome in different age groups. It is evident from table II that maximum incidence of nephrotic syndrome was observed between 4-6 years of age and nearly two third (64.61%) of the cases were between
1-6 years of age group. Brenner (1982) and Barakat (1986) reported that 60% patients of idiopathic nephrotic syndrome belonged to age group 2-6 years. Mc Enery (1982) reported 74% incidence of MCNS between 2-7 years while Saxena et al (1987) observed that majority of patients of MCNS were of $\leq$ 6 years age (mean age 5.8 years). Mean age of onset observed in this study was also same (5.8 ± 2.65 SD years). Saxena et al (1988) had observed mean age 7.5 years in their study.

Vaishnav and Chaudhary (1983) reported 34.6% cases having age of onset between 1-3 years while in this study 23.08% cases were observed in same age group. They observed 30.8% cases between 4-6 years age group while in study 41.53% cases fell in this group of age which is a little higher. But over all Vaishnav et al (1983) observed 62.4% cases between 1-6 years of age which is almost similar to observations of present study (64.61%).

Not all patients who came into contact for the first time were having onset of their illness from then only. 42 cases (64.61%) were having first episode of illness (Group A) and 23 cases (35.39 %) were in different stages of relapse (Group B – Table III).

Though many workers have commented upon clinical presentation of nephrotic syndrome, none of them have studied or compared the clinical presentation of patients with initial episode (Group A) and patients with relapse (Group B). As it is known that many times in relapse
stage classical clinical picture of nephrotic may not be there, we felt appropriate to study presentation of group B separately.

As presence of oedema is included in definition of nephrotic syndrome by International study of Kidney diseases in children and other workers its presence in all 42 cases (100%) with initial episode was natural but it was present in only 19 cases (82.61%) out of 23 cases of relapse (Group B).

As Rance et al (1976) defined relapse as oedema or 2+ reaction of urinary albumin for 7 consecutive days, it is clear that presence of oedema is not necessary for labelling it as a relapse. Trainin et al (1975) defined relapse as proteinuria 2+ for 3 consecutive days. But some workers have thought presence of oedema necessary for relapse. In our opinion patient can be in relapse even without evidence of edema. Though there is generalised oedema, in most of the nephrotic cases, it is the periorbital oedema which is commonest. As evident from table VI, it was present in all the cases (100%) of group A while in 82.60% cases of group B. Pedal oedema was present in 80.95% cases of initial episode and 60.87% of relapse cases. Anterior abdominal wall oedema was also elicitable in less cases of group B (52.17%) cases as compared to 71.42% cases of group A.

The second commonest presentation was complaint of passing less urine (oliguria) 37 cases (88.09%) of
group A had oliguria while its incidence was comparatively lower (73.31%) in group B cases (Table IV). Cause of oliguria is due to hypovolemia which is in turn due to decreased plasma oncotic pressure due to loss of albumin.

Diarrhoea or abdominal symptoms were third common complaint in this study group being present in 52.38% group A and 34.78% group B cases. Though its association with nephrotic syndrome is commonly reported, it has not been expressed in terms of percentage by now. Cause of diarrhoea could be usually intestinal wall oedema which is the part of generalised oedema. This may give rise to complaint of pain in abdomen also, in these patients. As incidence of oedema is less in group B patients. Incidence of diarrhoea was also expected to be less.

Fever was associated in 16.67% of group A and 8.70% cases of group B. Its presence can be explained by concomittant infection like UTI or ARI due to lower immunity levels.

Altered sensorium is form of drowsiness or apathy was evident in 9.52% cases of group A and 8.70% cases of group B, due to raised blood urea levels. One patient of each group (overall 3.08%) had convulsions due to hypertension.

Gross hematuria was evident in 7.14% cases of group A and 4.35% cases of group B, so chances of having hematuria was less in relapse. Gross hematuria was
uncommon in Minimal Change Nephrotic Syndrome (1.1%) as reported by McEnery et al (1983), while it was present in 20% cases of membranous nephropathy.

Table V depicts the relevant past history in both group A and B of present study. Special emphasis was given to elicit history for identification of secondary causes like drugs (captopril, probenecid, renographic medium), infections like malaria, syphilis, hepatitis and any cardiovascular cause or familial multi-system disorders but in none of present study group history of any of above factor could be elicited except for one case in which history of malarial pyrexia was there just preceding to onset of nephrotic syndrome (overall, 1.54%). While earlier workers have demonstrated secondary causes in 5-10%.

Nevertheless history of URI was present in 14.29% cases of group A and 39.13% cases of group B. Evidence of allergic episode like asthmatic bronchitis was there in 4.76% patients of group A and 17.39% cases of group B. In none of our cases there was preceding evidence of urticaria or bee sting.

Association of nephrotic syndrome have been reported with seasonal allergies by Cameron et al (1975) and atopic disease by Thomson et al (1974) but they have not indicated the percentage in their study.

Meadow et al (1981) searched for such provocative factors and observed that onset of syndrome or relapse
was often linked with a cold or a runny nose by the parents. In few cases it was clearly a viral infection affecting others in family. If such cases had been included as examples of allergic rhinitis (which they may be), the incidence of atopy in nephrotic children would have gone very high. This was quite high 49% in relapse cases and 25% in initial episodes in study conducted by Meadow et al (1981).

Evidence of cutaneous infection was present in 9.23% cases of all groups, of this study significance of which could not be ascertained as they have not been thought to be a provoking factors by the previous workers.

Fluid ultimately collects in pleural and peritoneal cavities. Ascites was elicitable in 54.76% cases and pleural effusion in 4.76% cases of group A and 43.48% and 0% cases of group B (Table VI).

Fluid collection was less in all instances in group B as oedema is also in lesser cases in this group.

Above figures could not be compared in absence of literature.

Due emphasis could be given to note anemia which was present in 73.84% cases (even with haemococoncentration presumed to be due to associated hypovolemia), and hepatomegaly in 43.07% cases. High percentage of anemia may be due to poor nutritional status of children in this backward region.
Hematuria was present in 21.53% of cases (Table VII). Habib et al (1971) reported it to be present in 13 to 29% cases, while White (1971) reported it in 13% cases. These observations are nearly same as present study, but Saxena et al (1988) had reported hematuria in 48% cases of nephrotic syndrome which is quite high as compared to the findings of present study.

Hypertension was reported to be present in 9% by White (1971), ISKDC reported it to be in 6 to 13% cases and that too mild and transient. Rance et al (1976) reported it in 9% in uncomplicated nephrotic syndrome. Saxena et al (1988) reported it to be present in 50% of cases which was quite higher as compared to present study (20%). Sonjakuster (1990) reported hypertension in 19% cases almost like the findings of present study (20%) but according to Bohlin et al (1984) it is not present in any case of MCNS.

Azotemia was observed in 18.46% of cases in present study. Saxena et al (1988) reported it in 28% cases which is relatively higher.

Mc Enery et al (1982) observed raised blood urea and serum creatinine levels in nearly 29% children with MCNS. This alteration in glomerular filtration is thought to be secondary to hypovolumia and restores following diuresis and resolution of proteinuria in those patients.

UTI was traceable in 15.38% cases of present study; which might be the cause of fever in most of the
patients. No comparison could be tried as none has presented the percentage of UTI. There was no evidence of multisystem disorder like SLE, Henoch–Schönlein purpura, Amyloidosis etc. in cases of present study.

An attempt was made to study the seasonal incidence of disease. Table VIII depicts that maximum patients had onset or relapse of their illness in October-December (32.30%) followed by July-September (29.23%). So nearly two thirds of patients were seen in July-December. 21-53% cases were seen in January-March and the least in April-June (16.92%).

Not much workers have tried to establish any seasonal factor except Reeves et al (1975) and Meadow et al (1981). As there is history of URI and allergic rhinitis in patients of nephrotic syndrome, it was thought whether it has some relationship with allergens prevalent in particular season. Though Meadow et al (1981) could not relate seasonal factor to onset of nephrotic syndrome and found that onset was distributed throughout the year, they also observed that onset was less common in April, May and June (9%) which is similar to findings of present study. They noted highest incidence in July-September (32%). Overall their observation was similar to present study in this respect that onset is less in summer months and more in winter months. Reeves (1975) noted that seasonal nephrotic syndrome does occur. If at all there is some relationship, it needs further investigation regarding
correlation of seasonal pattern of pollen allergy, house dust, mites, because workers have noted serum IgE tends to be higher in these children.

Among 23 cases of group B patients, who had history of similar complaints in past also, it was observed that 52.17% cases had experienced once, 30.43% cases twice and 8.70% cases 2 or more relapses (Table IX).

By definition of nephrotic syndrome, serum albumin levels less than 2.5 gm% and serum cholesterol more than 200 mg% are part of diagnostic criteria. Though previous workers have observed fulfillment of above criteria in majority of patients, yet exact figures are not available for comparison. In patients with initial episodes, serum albumin levels were <2.5 gm% in 96.24% cases but rest also had low serum albumin levels.

Estimation of 24 hour urinary protein protein was done in each case and in 6.15% cases proteinuria was < less than massive ( >7150 mg/kg/day or >40 mg/m²).

Majority of patients had proteinuria in range of 100-150 mg/kg/day (43.08%). Only 21.53% cases had >7150 mg/kg/day proteinuria (Table XI).

Prasad et al (1980) reported massive proteinuria >70.5 gm% in 57.1% cases and serum albumin levels <3.0 gm% in 57.1% cases. They observed serum cholesterol >300 mg% in 74.2% cases while in present study, only 39% cases had serum cholesterol beyond 300 mg%.

Except for Prasad et al (1980) no worker had observed percentage of c- in different ranges. Low
serum albumin levels (≤2.5 gm%) were observed in only 65.22% of cases. Serum cholesterol levels were raised in 92.86% of cases with initial episodes and 65.22% with relapse.

So in relapse cases, both clinical as well as biochemical derangements are less as compared with initial stage. This observation was not probably reported in literature.

In present study, raised blood urea levels 740 mg% was observed in 18.46% of cases. Prasad et al (1980) had observed this figure to be 28.5%. While serum creatinine was found raised in 20% of cases in present study. Prasad et al (1980) observed these figures to be 14.4% cases. ISKDC reported this figure to be 15% in MCNS and Saxena et al (1988) in 28% of cases. Azotemia was transient in most of these cases.

As MCNS is known to be the commonest lesion in nephrotic syndrome in children, it was not advisable to perform renal biopsy in every patient.

Age more than 1 year or less than 6 years, absence of hematuria and azotemia response to steroids are characteristic features of MCNS. These patients (40) were 61.54% and (25) 38.46% cases were those who did not fulfil above mentioned criteria so they were selected for renal biopsy (Table XII).

Bernstein et al (1982) opined that renal biopsy is usually not indicated in children with steroid sensitive
nephrotic syndrome. It was policy of Mcdonald et al (1976) to do biopsies in those nephrotic syndrome children who were less than 1 or more than 6 years of age or who fail to respond to initial 2 weeks of cortico-steroid therapy. On above criteria they felt need to biopsy $\geq 40\%$ of the nephrotic children. Besides that we thought it necessary to undertake biopsy in patients who were relapsing frequently, had developed steroid toxicity and induction of cytotoxic drug therapy was being considered. With all above considerations in mind we ventured for percutaneous renal biopsy in 25 patients (38.46\%) of our study group (Table XII).

MCNS was the commonest lesion even in cases with atypical presentation. Among 25 cases who were biopsied, 12 (48\%) still turned out to be MCNS. Meadow et al (1981) who chose patients for biopsy on similar pattern reported that in 50% cases who were biopsied lesion was MCNS in rest biopsy was not under taken as they were unlikely to show histological lesion other than MCNS, because their clinical course and findings were even more typical of MCNS than those who underwent biopsy.

Overall minimal change nephrotic syndrome (MCNS) was lesion in 52(80\%) cases. Among them 40 had typical clinical presentation while 12 were diagnosed after biopsy. Previous workers Habib et al (1971) and ISKDC (1978) reported it to be present in 52-78\% of idiopathic nephrotic syndrome cases, while Saxena et al (1988) reported it in
68.3% cases. Other workers have reported it in 85% cases.

In the present study, mean age of MCNS cases was 5.49±2.65 years, almost similar to 5.2 years as reported by Saxena et al (1988) and 5.8 years as described by other workers. Hematuria was observed in 11.53% cases in the present study. Habib et al (1977) described it in 13 to 29% of cases while Rance et al (1976) observed it in 13% cases and Saxena et al (1988) in 40% cases. Gross hema-
turia was very rare, 1.1% observed by Cameroon (1978) and 1.4% as observed by Saxena et al (1988). 13.48% cases of MCNS in present study group turned out to be hyper-
tensives as against 9% observed by Rance et al (1976). Habib et al (1971) and ISKDC (1978) described it in 6-13% cases and Saxena et al (1988) in 35.5% cases. But hyper-
tension was mild and transient in majority of cases.

Findings of present study are in accordance in of previous workers except Saxena et al (1988) in this regard. Azote-
mia was observed only in 7.69% of MCNS cases. Rance (1976) noted it in 4% cases. Saxena et al (1988) too observed normal mean values of blood urea and serum creatinine cases in MCNS.

As depicted in table XIII, focal glomerulo-
sclerosis (FSGS) was found in 4(6.15%) cases. Marginally higher incidence (in 10%) was reported by Cotran et al (1983). Saxena et al (1988) observed FSGS lesion in 10.6% cases of their biopsies group of patients. Relatively
lower percentage of FSGS cases in present study can be explained by the fact that many FSGS patients responded to steroids favourably and so there is a possibility of including one or few with typical MCNS thereby avoiding consideration for biopsy. Besides this it is disputed by some workers whether it is a separate entity at all or not. In fact Churg et al (1970) brought this entity to light from those patients in which steroid response was relatively poor. Waldnerr (1983) is of opinion that it represents variation of MCNS rather than separate entity. Goldzer et al (1984) disputes whether FSGS represents a distinct disease or is simply a phase in evolution of a subset of patients with lipoid nephrosis. Patient showing MCNS in first biopsy may subsequently show focal segmental glomerulosclerosis (FSGS). Besides this as the lesion is focal and changes are present in juxta medullary glomeruli chances of missing some cases of FSGS on biopsy cannot be ruled out. Mean age observed for this group was 6.15 years which is little higher. Almost similar observations were also made by Saxena et al (1988) who noted mean age in FSGS to be $9.857 \pm 2.795$ years. Rance et al (1976) also observed the same. Rance et al (1976) observed hematuria in FSGS to be 66%. Cameron (1968, 1973), Glasgow (1971), Nash et al (1976) also observed higher incidence of microscopic hematuria in FSGS (50-90%). Gross hematuria was not thought to be that common in this group. This is in accordance of the observation of hematuria in 50%
cases of FSGS in present study.

Hypertension was observed in 25% cases of FSGS in present study, while Rance et al (1971) had observed it in 10% of FSGS cases and Saxena et al (1988) observed it in 85.7% of cases. So observation of present study lies in between of these two extremes, but definitely hypertension was relatively common in FSGS as compared to MCNS.

Azotemia to be prevalent in more, was observed by almost all workers. Rance et al (1976) observed it in 10%, while Cotran et al (1983) observed it in 25% cases. Saxena et al (1988) ascertained significantly higher values of serum creatinine and blood urea in FSGS. Azotemia was observed in 50% cases of present study.

In fact importance of this lesion was relative lack of response to steroids and progression to end stage renal disease as described by Churg et al (1970).

Membranoproliferative glomerulonephritis was observed in 4(6.15%) cases in present study as against 10% by Cotran (1983). Saxena et al (1988) observed it in 13.6% cases. Mean age observed in present series was definitely higher 9.25 years as compared to 5.49±2.65 years of MCNS group. Saxena et al (1988) had observed mean of 9.556±1.740 years. Earlier workers have described it to be most common lesion in 2nd decade. Microscopic hematuria is very common and almost in all cases even gross hematuria is not rare. Rance et al (1971) noted gross hematuria in 20% and microscopic in 68% cases. In present series hematuria was present in all 4 cases of membranoproliferative-
tive glomerulonephritis. Hypertension was present in 75% cases of membranoproliferative glomerulonephritis in present study while in 25% cases in study of Rance et al (1976) and in 88.8% in study of Saxena et al (1988).

In most of the cases of present study in membranoproliferative group, hypertension was not transient and required specific drug therapy.

Azotemia was common in membranoproliferative glomerulonephritis (50%) in present study as compared to 31% cases of Rance et al (1976).

In present study, 4.16% cases on light microscopic examination there was only slight diffuse increase in mesengial cells and cell matrix and thickening of mesengial shock. Capillary wall and interstitium was normal. This lesion was first described by Drunmond et al (1966), and well recognised by Churg et al (1970). Habib et al (1973) described this lesion in 2.5 to 5.3% of cases. Other workers also described it in 5% of cases. In present study, hematuria, hypertension and azotemia was present in 33.33% cases. Worekrs have described this lesion clinically indistinguishable from MCNS except for older mean age (White, 1970) and higher incidence of Hematuria. Brown et al (1979), Trainin et al (1975) described hematuria in 36 to 100% cases. It's close resemblance to MCNS have prompted workers to classify mild to moderate, mesengial proliferation as MCNS. Newman et al (1976) have said that some of these patients may
subsequently develop FSGS. Mean age in present study was 6.5 years as compared to 5.49±3D years of MCNS. In membranous nephropathy was present in 3.08% of present series, while Saxena et al (1988) reported it in 7.5% cases. Hematuria was commoner (50%) which is in accordance of other studies. Rance (1976) reported it microscopic hematuria in 70% and gross in 20%. Saxena et al (1988) reported hematuria in 60% of cases and hypertension in 60% cases as compared to present study 50%. Cotran et al described it in 15-35% cases. Mean age observed in present work was higher 9.25 years as compared to 5.49 years in MCNS and 7.6±1.941 years for same lesion by Saxena et al (1988). In this series azotemia was commoner (50%). Saxena et al (1988) also observed similar findings.

An attempt was made to study the pattern of response to steroids in correlation of histopathologic lesion. The response pattern was grouped in four categories.

Group B comprised non responders, group C frequent relapsers and group D included steroid dependent. Group A comprised responsive pattern other than above mentioned. Majority of them were responders and typical of MCNS type.

It was an endeavour to biopsy as many cases as possible with atypical steroid response, so that underlying pathology could be ascertained. Among non responder (Resistant) group all 6 cases were biopsied and among them
2 cases were of membranoproliferative and 1 (16.67%) case of membranous variety. Prasad et al (1980) demonstrated minimal lesion in 20% cases of steroid non responders and mesengial proliferative lesion in 25% cases and membranous lesion in 20% cases and membranoproliferative lesion in 35% cases. Those findings are though not exactly but basically correlate with our findings. Training (1975) observed that 10% cases of MCNS would turn out to be steroid resistant, while in present series 2 out of 52 (3.85%) MCNS cases turned out to be non responders. In both of these cases age of child was more than 7 years as observed by ISKDC (1981), that in all probability non responder cases if turns out to be of MCNS type on biopsy shall be more than 7 years age. 3 out of 4 (75%) cases of membranous proliferative group were steroid resistant while 50% of membranous glomerulonephritis cases were steroid resistant. This high percentage of response in these groups was described by all previous workers but no any proven cases of FSGS could be found to be steroid resistant in the present study.

As ISKDC (1974) has described that 25% cases of MCNS will relapse frequently. In 10 out of 13 (76.92%) cases of frequent relapsers, biopsy was possible and out of those 10 cases 60% had minimal changes lesion while 20% each had FSGS and mesengial proliferative lesion. It has already been described that among frequent relapsers 50% cases were of minimal change disease.
According to our observation 50% cases of FSGS were relapsing frequently i.e. very high percentage and 2/3 cases of mesangial proliferative group were also frequently relapsing. Abramowicz et al (1970) and other workers had observed that many of biopsy proven FSGS cases will become frequent relapsers and steroid dependent and develop late steroid resistance. As we followed our patients for maximum 24 months, we were unable to elicit late steroid resistance in FSGS cases. We could biopsy 4 out of 6 (66.67%) cases with steroid dependence and 2(50%) of them were MCNS and 25% each of FSGS and membranous type.

Immunological abnormalities in nephrotic syndrome are being analysed for long time. Reduced concentration of gammaglobulins in serum of patients with nephrotic syndrome was reported as early as 1940 (Longsworth, 1940). Subsequently decreased levels of IgG have been observed in patients of idiopathic nephrotic syndrome irrespective of the course (Giangiacoma, 1975). As evident from table XIV mean concentration of serum IgG 853.38± 276.53 mg/dl is lower as compared to control's 1777.50± 124.73 mg/dl and this is statistically highly significant (p < 0.001). IgG levels in nephrotic syndrome children were 48.01% that of controls.

Andal et al (1990) also reported low serum IgG levels at the onset (p < 0.001). They also observed 48% fall in serum IgG levels.
Mehta and Ali et al. (1985) reported low serum IgG levels at relapse as well. In their study serum IgG levels were 576±164.1 mg/dl in cases and in controls 1072±34.85 mg/dl (p < 0.001). Yokoyama et al. (1985) and Sudhir Gupte et al. (1985) too reported low IgG levels. This depression in IgG cannot be explained on urinary losses alone. Increased catabolism may play a part. It has been postulated that T cell mediated conversion from IgM to IgG synthesis may be defective. It has not been established whether the depression in cell mediated immunity is a primary event or secondary to hypoalbuminemia, hyperlipidemia or zinc deficiency that co-exists in these patients as all these factors are known to depress cell mediated immunity.

In present study there was concomitant statistically significant rise in IgM levels. From 209.25±54.06 in controls to 300.57±72.01 mg/dl in nephrotic patients (p < 0.05). Significant rise in serum IgM levels was also reported by Sudhir Gupte et al. (1985), Yokoyama et al. (1985) and Andal (1990). Andal et al. (1990) reported serum IgM levels to be 303.1±112.4 mg/dl in nephrotic syndrome versus 169.0±89.1 mg/dl in controls. In present study there was 143.6% elevation in IgG as compared to 163% observed by Andal et al. (1990). Concomitant elevation of IgM with lowering of IgG may be related to the fact that nephrotic syndrome primarily a thymic cell dependent immune defect. Cells which normally produce IgM class of antibody
before converting to the synthesis of IgG and IgA fail to elicit response thus resulting in elevated levels of IgM (Davie et al, 1974). Similar observations were made in this present study.

In complement studies, there was no significant difference observed in levels of C4 between nephrotic patients and controls while there was lowering in serum C3 levels by 18%. They were observed to be 107.75±35.39 mg/dl as compared to 130.25±15.99 mg/dl in control group statistically insignificant (p > 0.2). The reason being that in MCNS serum complement levels remain normal by and large and majority of patients were of MCNS type in present study. Various workers have observed no changes in C3 levels in MCNS.

Rance et al (1976) and Mehta and Ali (1985) reported that serum complement levels are generally normal in MCNS. Prasad et al (1980) reported initial hypocomplementemia in 9% of their MCNS children but in none of them it was persistently low. As obvious by table XV, 7.7% MCNS children had initial hypocomplementemia and similarly none of them had persistently low levels. Overall 20% children had initial hypocomplementemia as compared to 32% observed by Prasad et al (1980). In the present study persistently low levels were observed in 6.15% cases as compared to 8% of their. In present series all 4 children with membranoproliferative lesion had hypocomplementemia in the beginning and persistent in 75% children. Rance
et al (1976) reported hypocomplementemia in 68% cases of MPGN and Prasad et al (1980) reported initial hypocomplementemia in 83.3% children and persistent hypocomplementemia in 50% cases of MPGN.

In mesangial proliferative group Prasad et al (1980) observed hypocomplementemia in 87.5% cases and persistent in 12.5% of them, while in present work, initially low levels were observed in 66.67% cases and persistently low levels in 93.3% cases. Saxena et al (1988) too observed hypocomplementemia in all MPGN cases. In focal and segmental glomerulosclerosis and membranous nephropathy none of the patients had persistently low C3 levels though few had initially low levels as observed in present study.

West (1965) and Ogg (1968) suggested that persistent hypocomplementemia is characteristic of a discreet group of patients with poorly selective proteinuria.

In 4 patients of MCNS who had initially low C3 levels. Two turned out to be steroid dependent and 2 developed late steroid resistance so low C3 levels observed in MCNS can be related with altered steroid response later. None of the low C3 level cases of MCNS suffered frequent relapses.

Thus the measurement of serum levels of specific components of complement system is helpful in the diagnosis of 6 various types of nephropathies and in evaluation of therapy.
It was also tried to study the incidence of tuberculosis in nephrotic syndrome (Table XVII) and further analysis whether this has any bearing with steroid response pattern. This was thought necessary as tuberculosis infection is widely prevalent in our set up, and it has already been proved by Molean et al (1977) and Vaishnav et al (1983) and other workers that presence of active though subtle infection may be responsible for steroid resistance in MCNS and even relatively slow response.

Twelve (18.46%) cases of present study group had evidence of primary complex. This was considerably higher than incidence of tuberculosis in children described as 2.7% by Dingley (1976). Vaishnav et al (1983) had observed evidence of tuberculosis in 10% of their group of nephrotic syndrome children while Prasad et al (1980) had described it in 35.38% cases before therapy and 10% cases after therapy so our incidence lies between these two and it is definitely higher than usual population, cause of which is to be ascertained. Among our patients with pulmonary tuberculosis/primary complex 66.67% cases had not received steroids earlier, indicating that this higher incidence of tuberculosis was not mainly due to flaring up of hidden tuberculous focus during therapy.

Further an attempt was made to elicit possible effect on steroid response, as shown in table XXIII. Patients of present study were divided into two groups.
Group A (patients responding within 2 weeks which had incidence of tuberculosis in 8.7%) and group B (patients responding after 2 weeks) which had incidence of tuberculosis in 33.33% which indicated that presence of chronic infection like tuberculosis should be searched in patients who showed relatively slower response to steroids. It has been already discussed that presence of infection can result in slow or no response to steroids. Among frequent relapsers incidence of tuberculosis (23.07%) was little higher than in our whole study group (18.46%) which does not seem to have any bearing. So it can't be said whether frequent relapsers have any relation with underlying tubercular infection. Vaishnav et al (1983) have also correlated slow response to steroids with underlying tubercular infection but difference between the two studies is that they had taken slow responders as who respond after 8 weeks as compared to two weeks in the present study.

In 96.92% cases of present study steroid was used for induction of remission while in rest (3.08%) it was achieved spontaneously (Table XVIII). For maintenance of remission steroids were used in 68.25% cases of present study while in 31.75% of cases this was not required. Cyclophosphamide was used in 12.31% cases for induction and in 12.50% cases for maintenance of remission in the present study.
Though spontaneous remission is described in cases of membranous nephropathy, percentage was not observed previously.

Different patterns of steroid response have been described by various workers and ISKDC. We had endeavoured to group our patients in these categories and compared them with previous workers observations (Table XIX). Out of 65 cases, 2(3.08%) achieved remission spontaneously and among rest 63 cases, 96.92% were initial responders. These were the patients who responded during first 8 weeks of steroid therapy.

3.17% cases were early non responders while 6.15% cases turned out to be late steroid non responder.

Trainin (1975) observed that 5-10% cases of MCNS are early non responders while 5% turn out to be late non responder. Lesions with focal glomerulosclerosis and mesengial proliferative are known to develop late steroid resistance. Grupe (1979) estimated late steroids resistance in 4.8% and Srivastava et al (1986) in 3% cases. Six cases (9.23%) of our study were steroid dependent.

Abramowicz et al (1970) has ascertained that more cases of FSGS will become steroid dependent but percentage has not been described.

Slow responders are that group of patients in whom proteinuria become less but did not disappear within 8 weeks of steroid therapy, though eventually disappears completely (Vaishnav et al, 1983).
An attempt was made to group the patients according to response time, which is the interval between the initiation of treatment and first day of traces or nil reaction for urine albumin.

But as under our observation majority of cases (75.40%) respond within 2 weeks of initiation of steroid therapy. So we have used the term 'relative slow responder' in which those patients were included who responded after 2 weeks of steroid therapy.

Twenty percent of our cases were frequent relapsers, while in ISKDC (1978) 25% children of MCNS are said to be frequent relapsers and this percentage is still higher in focal glomerulosclerosis group in our study it was 11.53% cases of MCNS were frequent relapsers (all biopsy proved) and 50% cases of FSGS were F.R. (biopsy proved).

75.40% cases responded within 2 weeks of steroid therapy among these 22.95% responded within 1 week and 52.45% between 1-2 weeks (Table XX). It has been described in previous studies also that most of the children begin to respond to corticosteroid regimen within 14 days of treatment (Mc Enery et al, 1982).

According to ISKDC (1976) all nephrotic children who were going to to respond to prednisolone 73% did so within 14 days and another 21% in next 14 days of initial steroid therapy.
In this study 8.19% cases responded between 3-4 weeks and 3.28% cases responded between 4-5 weeks and 1.64% cases responded between 5-8 weeks of initiation of steroid therapy. So over all 24.60% cases were labelled as relative slow responder by us. None of the previous workers have classified their cases in this fashion.

It was tried to estimate relapse free interval after remission was induced by steroids or cyclophosphamide (Table XXI and XXII).

Relapse free interval was ≤2 months in 6.15%, 2-4 months in 10.77%, 4-6 months in 18.46% and 6-12 months in 21.54% and 12-24 months in 36.92% cases. So maximum patients (24) were free from relapse for 1-2 years after remission was induced but more than 2 years relapse free period was present in only 6.15% cases as our study period was only 24 months, we estimated these figures by retrospective figures also. None of previous workers have studied response to steroids in this way, except that they described that majority (90%) of MGNS cases suffer relapses and 25% of them frequently (ISKDC, 1974).

Similarly among 8 cases in which cyclophosphamide therapy was administered, 2 were free from relapses for ≤6 months and 2 for 6-12 months and 4 (50%) for >1 year. Previous studies have also described longer remission on cyclophosphamide therapy. Sixty five percent patients have been estimated to remain in remission for more than 5 years and in 50% cases permanent remission was noted. Due to
short study period we could not corroborate these observations. (Chiu et al (1973), Moncrief (1969) showed that 25% children did not had a relapse within 1 year of treatment as compared to 50% in our observations and 50% did not relapse for 2 years.

Early identification of frequent relapsers has always posed problems. Attempts to correlate prediction of frequent relapsers with hematuria, hypertension and azotemia have not been useful and attempts to correlate course of the disease with the histologic findings have met with only limited success. So we attempted to review a report of ISKDC (1982) in which number of relapses in first 6 months of onset was correlated with future course of disease. We observed that among patients who did not suffer any relapse in first 6 months (44.61%) only 3.45% developed frequent relapses while among 6.15% patients with 73 relapses in first 6 months 50% had frequent relapses in subsequent course (Table XXIV). ISKDC (1982) underlined absence of a relapse during first 6 months – the initial response proved to be an excellent clinical predictors of a favourable course during the first 2 years. Occurrence of 73 relapses during initial 6 months period can be used clinically to predict a frequently relapsing course.
Various types of steroid response in nephrotic syndrome have already been discussed and also their correlation with histopathologic lesion. In table XXV an attempt was made to correlate steroid response with clinical features.

In children \( \leq 6 \) years age 22% patients were frequent relapsers, while resistant (2.27%) and dependent (6.82%) cases were less. In contrast to this resistant (23.08%) and dependent cases (14.29%) were common in age group 7-6 years and frequent relapsers were slightly less (14.28%). Hypertension and hematuria and azotemia were more commonly associated with steroid resistance, but not with steroid dependency.

Cases were followed up carefully to study response pattern and relapses and number of patients registered suffered relapses during 2 years study period and in these episodes of relapses we observed history or evidence of URI in 28%. Allergic episodes like allergic rhinitis in 21%, UTI in 4%, other infections in 7%. In 40% cases none of the above or known factor was there. URI and allergic episodes are already been discussed as possible factors having potential bearing over occurrence of relapse as also seen by Meadow et al (1981). They also observed like us that a nasal discharge was a frequent precursor or accompaniment of nephrotic syndrome. Meadow (1981) observed that 50% patients had history of at least
relapses twice within 3 days of such URI. In 50% patients relapse was always associated with a cold. In some cases history suggestive of communicable viral cause was elicitable.

Though in our study group this observation had not as high incidence as of Meadow et al (1981) but it was still significantly higher to think on same lines. The difficulty was that despite careful questioning no provocative factor could be found to account for runny nose. It was interesting that runny nose was not common in children who had single bout of nephrotic syndrome. As raised IgA levels are also known in nephrotic syndrome patients this would lead to identification of certain factors, if avoided could lead to decrease in relapses or development of preventive measures or drugs.

As shown in table XXVII, we have been able to establish very low levels of serum IgG levels (531.38 ± 132.87 mg/dl) at onset in frequent relapsers as compared to 938.07 ± 250.30 mg/dl in infrequent relapsers and this difference was statistically highly significant (p < 0.001).

Infrequent relapsers were also having highly significant low levels of IgG as compared to control group (p < 0.001). This observation was in accordance with Andal et al (1990) who had noted the same in their study. But in present study serum IgM levels were significantly higher in frequent relapsers as compared
to infrequent relapers ($p < 0.05$), while Andal et al had though observed higher IgM levels in frequent relapers but this elevation was not found statistically significant. So, very low IgG and high IgM levels can serve useful predicting marker for frequent relapers though Giangiacoma (1975) reported no change in immunoglobulin levels between frequent and infrequent relapers.